



THE UNIVERSITY OF ARIZONA  
COLLEGE OF MEDICINE TUCSON

Pediatrics



# The Seemingly Endless Scourge of Syphilis

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# Disclosures

- I have no conflicts of interest to disclose
- I will discuss non-FDA approved therapies (for historical purposes)

# Objectives

- Describe the history of syphilis
- Recognized the signs and symptoms of syphilis
- Discuss the state of syphilis in the US and Arizona
- Identify ways to prevent congenital syphilis

# A preterm baby with peeling skin and other abnormalities

- 28 weeks gestation
- Hepatosplenomegaly and elevated LFTs
- Thrombocytopenia
- Pleocytosis with positive CSF VDRL
- Mom noted to have condyloma lata at delivery



# Osteitis





Our patient



Normal xray  
(term baby)



Our patient



Normal xray  
(term baby)

# The sad history of syphilis

- Thought to have come from the New World
  - Syphilitic lesions seen pre-Columbian New World bones, but not in Old World bones from the same period
  - Described in Western Europe the year Columbus's voyage returns from Hispaniola
    - Crew noted to have symptoms of syphilis and noted to be present in the New World at the time of their voyage
    - Spread throughout cities visited by the crew and other explorers early on in the initial outbreak



# The Great Pox spreads throughout Europe

- Discovered early on that it was transmitted sexually
- Brought by sailors as well as soldiers and camp followers as they invade various countries
- More virulent at that time with a fairly high mortality rate for secondary stage
- Blame for the disease is spread around but the Spanish always call it disease of the Isle of Española due to suspected provenance of the disease
- Disease appears in Asia after visits from European explorers

# European syphilis pandemic

- Estimated 10-15% of the population of large cities in Europe infected in the late 1800s
  - Incurable disease
- Many famous people thought to have had syphilis

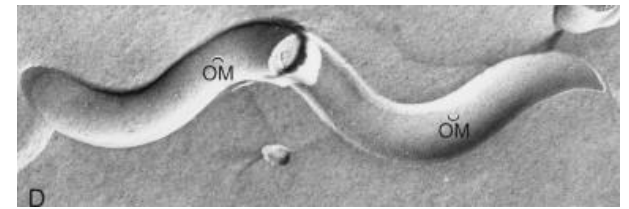
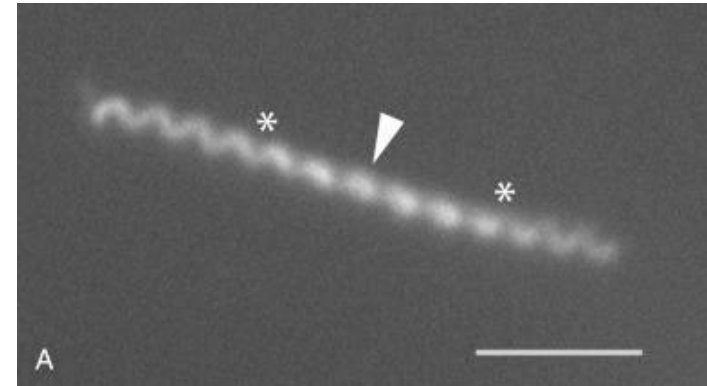
# Henry VIII and syphilis?

- May have had mental illness due to tertiary syphilis late in life
- Large ulcers down to the femur that were painful
  - Increased execution rate when in pain
  - Estimated to have executed 3% of the population of England during his lifetime



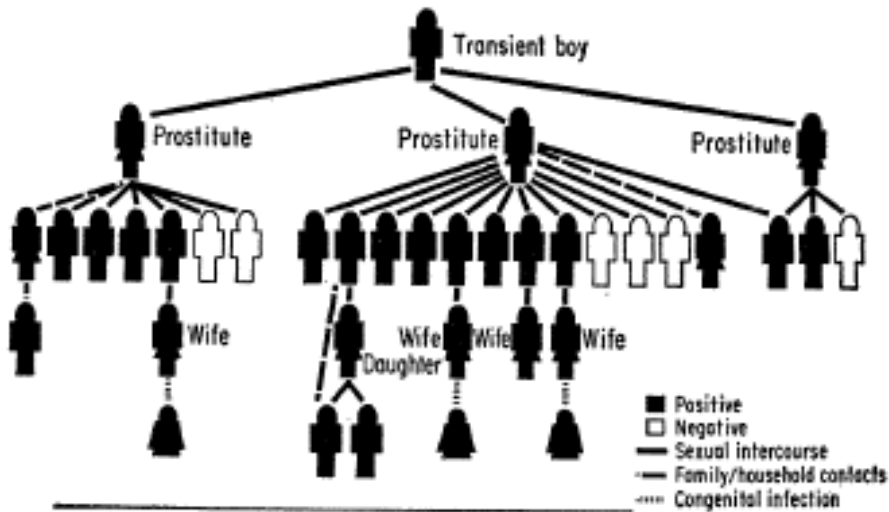
# Highly contagious

- Sexual transmission rate 30%
- Mother to child: up to 100% depending on timing of infection during pregnancy
- Fomite and mucous membrane contact possible but rare



# Impact

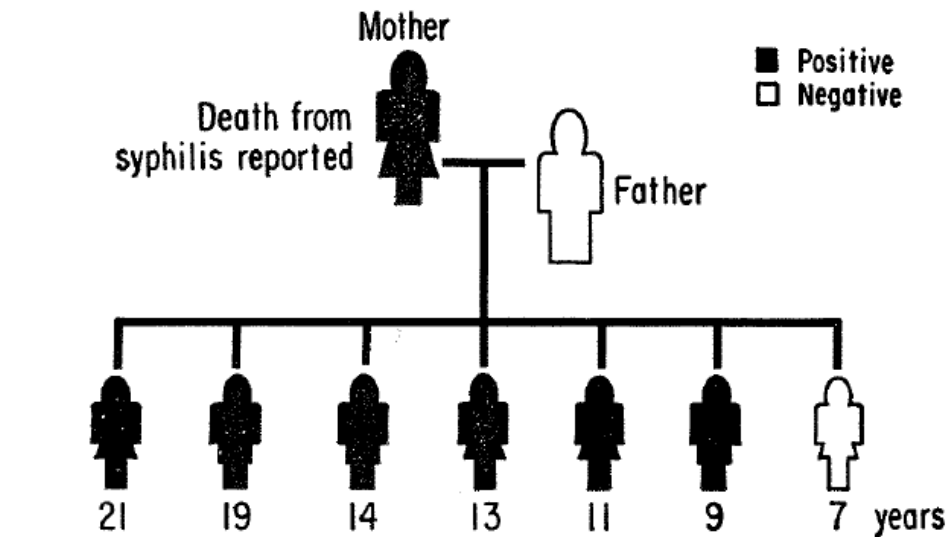
Outbreak of Syphilis in Monroe County, Tenn.



Data from Kimbrough, Cowgill, and Bowerman, Madisonville, Tenn.

Figure 5.

Congenital Syphilis

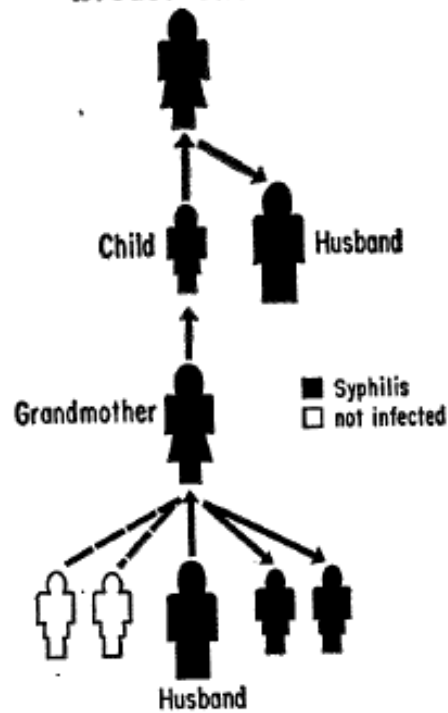


Data from New York City Health Department.

Figure 6.

# Impact

## Investigation of Contacts of WF with Breast Chancre



redrawn from Kompmeier

Figure 4.

# Manifestations

- Non congenital infection
  - Primary
  - Secondary
  - Latent
    - Early <1 year since infection
    - Late >1 year
  - Tertiary
- Congenital infection
  - Early
  - Late

# Non congenital Infection: Primary Stage

- 1-4 weeks after exposure
- Painless papule, erodes to a painless ulcer (chancre)
  - Can occur on the cervix or vagina and may not be noticed
  - Teeming with spirochetes
- Heals over 3-6 weeks





# Secondary stage

- 2-10 weeks after primary lesion
- Most symptomatic, “great imitator”
- Dissemination of the organism
  - Can involve any organ system, almost always involves skin/mucous membranes
  - Often mild/asymptomatic but can be severe
- Can get relapses over months to years
- Contagious: high degree of spirochetes in the lesions and blood

# Mucocutaneous Manifestations of Secondary Syphilis



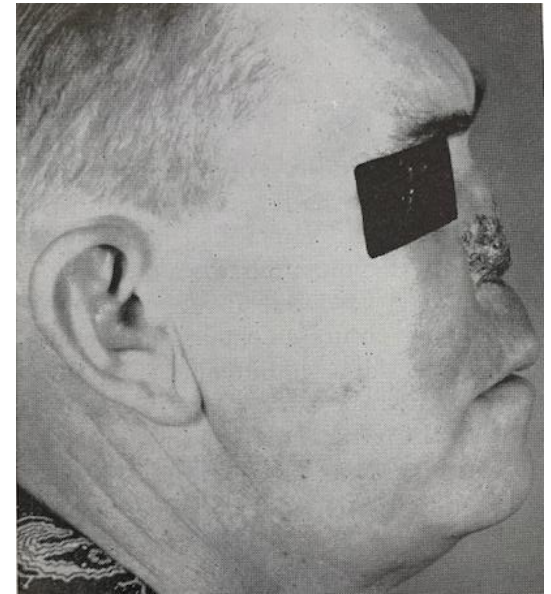
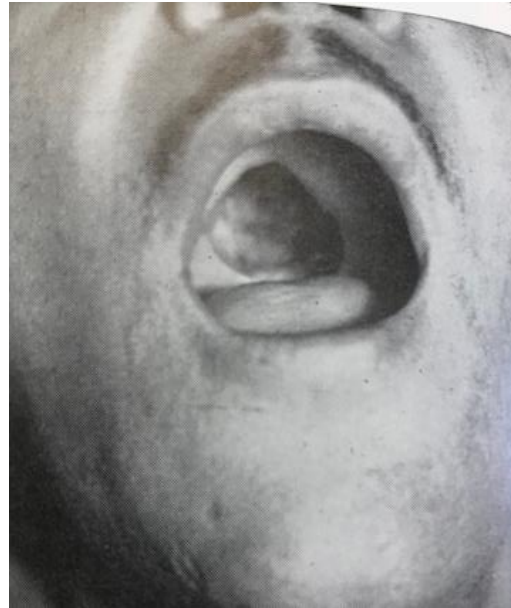
# Latent Stage

- No symptoms, but can relapse to active state and have symptomatic or asymptomatic episodes of spirochetemia
- Early latent <1 year since symptoms
- Late latent >1 year since symptoms

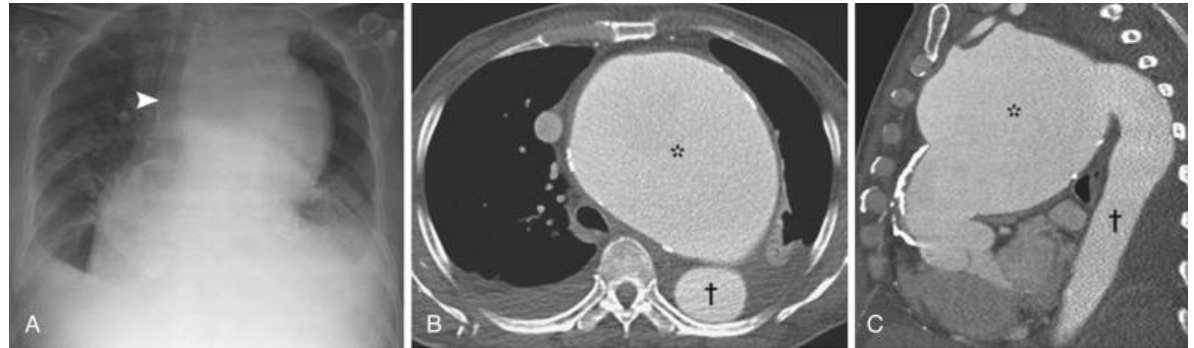
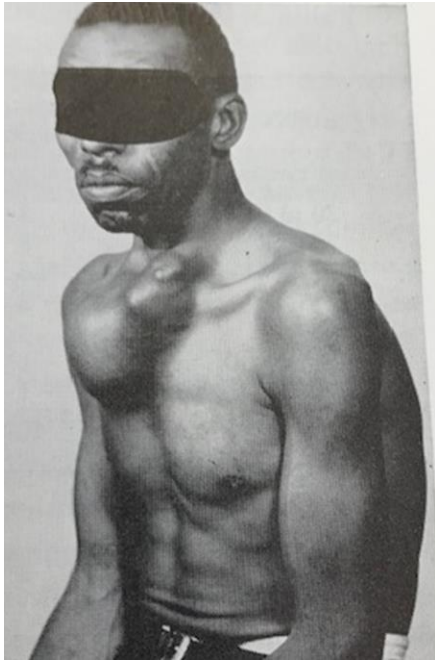
# Tertiary Stage

- 28% of untreated patients develop tertiary disease
- Some of the most dramatic manifestations of syphilis
- CNS
  - Meningovascular (stroke-like signs/symptoms)
  - Tabes dorsalis
  - Neuropathy (sensorineural hearing loss)
  - Generalized paresis
  - CNS Gummas

# Tertiary Syphilis: Gummas



# Tertiary Syphilis: Aortic Aneurysm





# Early “Treatments”

- Expensive extracts, oils, etc
- Mercury
  - Cure worse than the disease
    - Oral ulcers, tooth loss, renal failure, neuropathy, death
- Fever
  - Julius Wagner-Juaregg nobel prize
    - Plasmodium vivax
      - 15% mortality rate



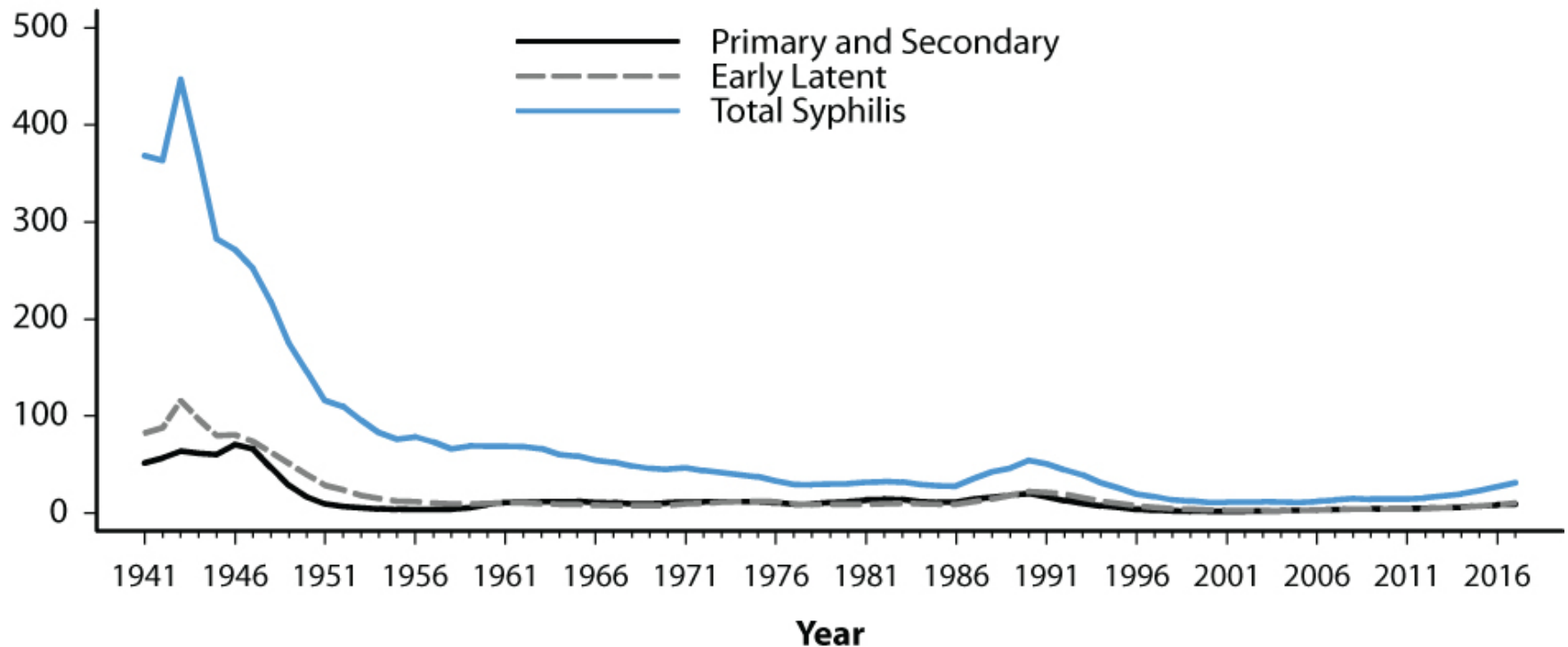
# Early “Treatment”

- Salvarsan (arsenic)
  - Paul Ehrlich’s lab- received the Nobel Prize
  - 1<sup>st</sup> treatment that could cure syphilis
  - High toxicity rate
  - Complex preparation and administration by injection
- Hospitalization until no longer contagious-ish



# Impact of penicillin and treatment programs

Rate (per 100,000 population)



# Tuskegee and syphilis: a shameful history of deliberate harm

- 1932: the US Public Health Service begins a natural history study on syphilis in Macon, AL
  - 600 African American men enrolled initially
    - Most were poor sharecroppers who didn't have good access to medical care
    - Were told it was an experiment for "bad blood" which could mean many things, including syphilis
  - Got free exams, meals and burial insurance
  - Penicillin wasn't available at that time

# Tuskegee and syphilis: a shameful history of deliberate harm

- Problems
  - No informed consent
  - Vulnerable population that didn't have access to good medical care
  - Participants were deceived into thinking that diagnostic lumbar punctures were in fact therapeutic
  - Not informed that autopsy would be performed at death
  - Communication between investigators riddled with racist, paternalistic, self-serving harmful ideas

# Tuskegee and syphilis: a shameful history of deliberate harm

- 1940s penicillin is used to cure syphilis and widely available
  - Study doctors deliberately withheld treatment
    - Worried they would never have this opportunity again to see what syphilis does to people
    - Told local doctors that they were on the study and not to treat them either
  - Study goes on with some results published from time to time in various journals
    - No one raises the obvious question of ethics until the late 1960s

# Tuskegee and syphilis: a shameful history of deliberate harm

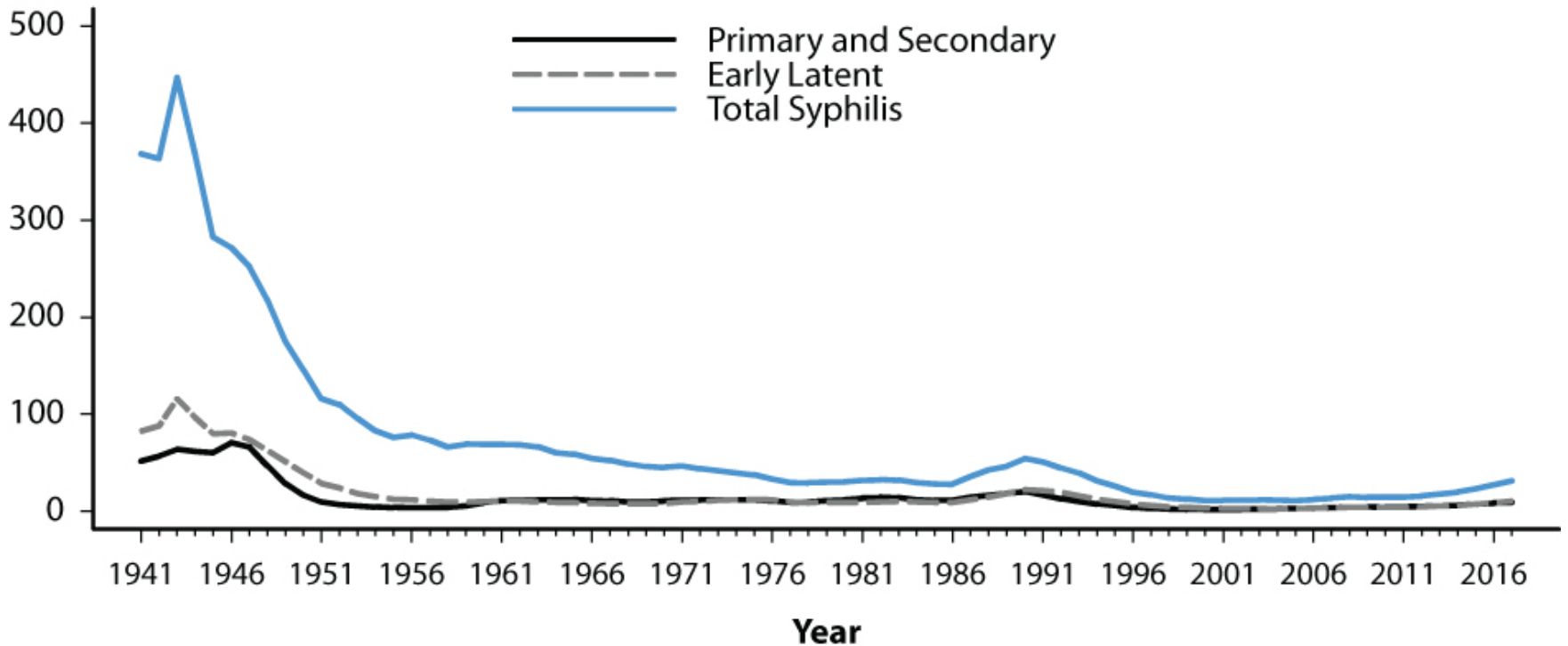
- 1972
  - Associated Press releases a story about the study
  - Study is deemed ethically unjustified by an ad hoc government advisory panel
- 1973
  - Study officially stopped
  - Class action lawsuit awards \$10 million to participants and families
  - Congress passes the National Research Act
    - Leads to the establishment of IRBs, informed consent and protection of vulnerable populations
- 1997
  - President Clinton issues formal Presidential Apology

# Tuskegee: Aftermath

- Estimated 100 men died of syphilis that could have been treated
- Widespread distrust of the medical and research community persists today
- Increased efforts to protect vulnerable populations and make research ethical and equitable

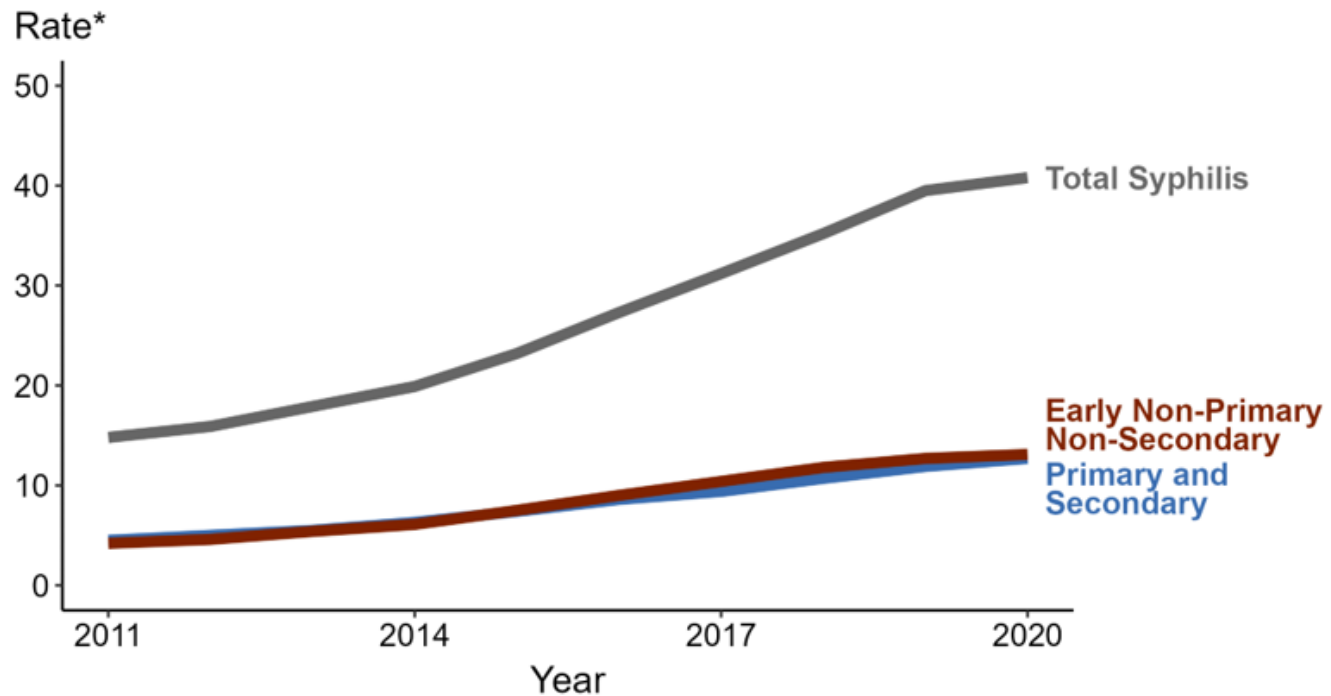
# Highly effective treatment available

Rate (per 100,000 population)



# But...syphilis is on the rise again

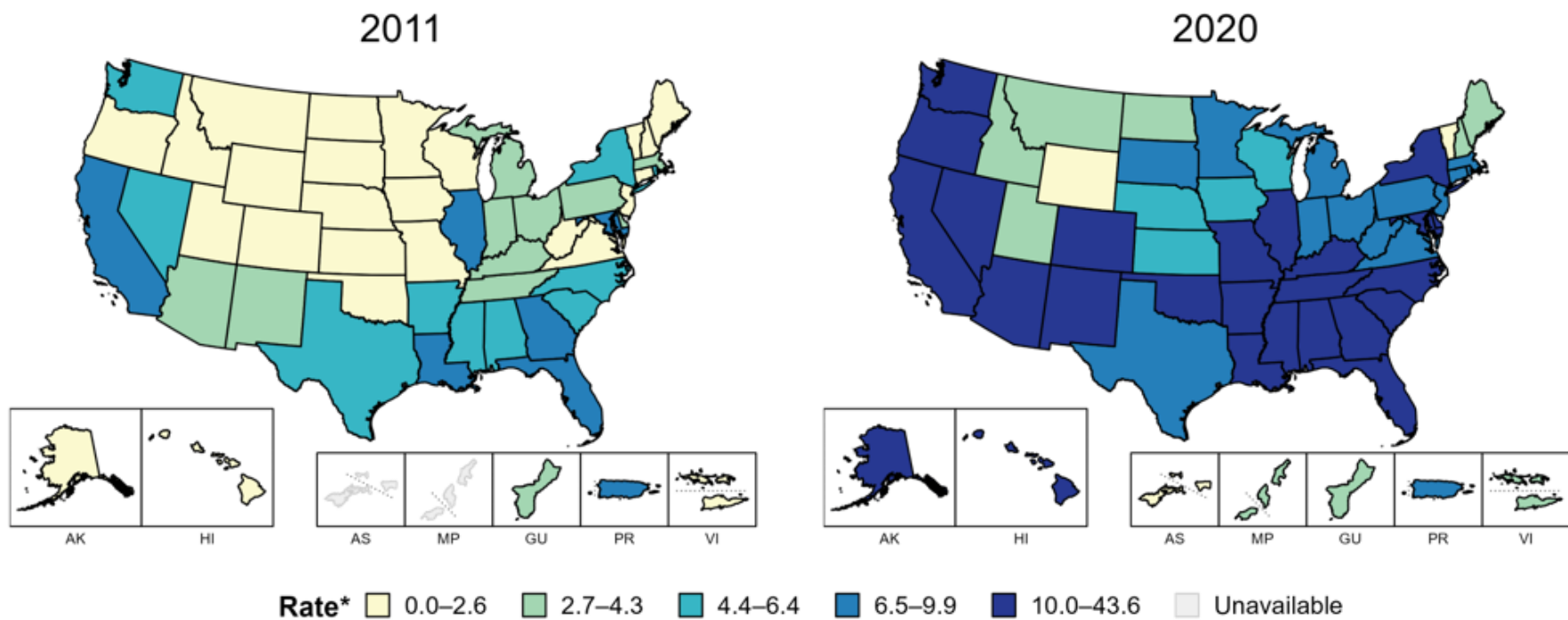
## Syphilis — Rates of Reported Cases by Stage of Infection, United States, 2011–2020



\* Per 100,000



# Primary and Secondary Syphilis — Rates of Reported Cases by State, United States and Territories, 2011 and 2020



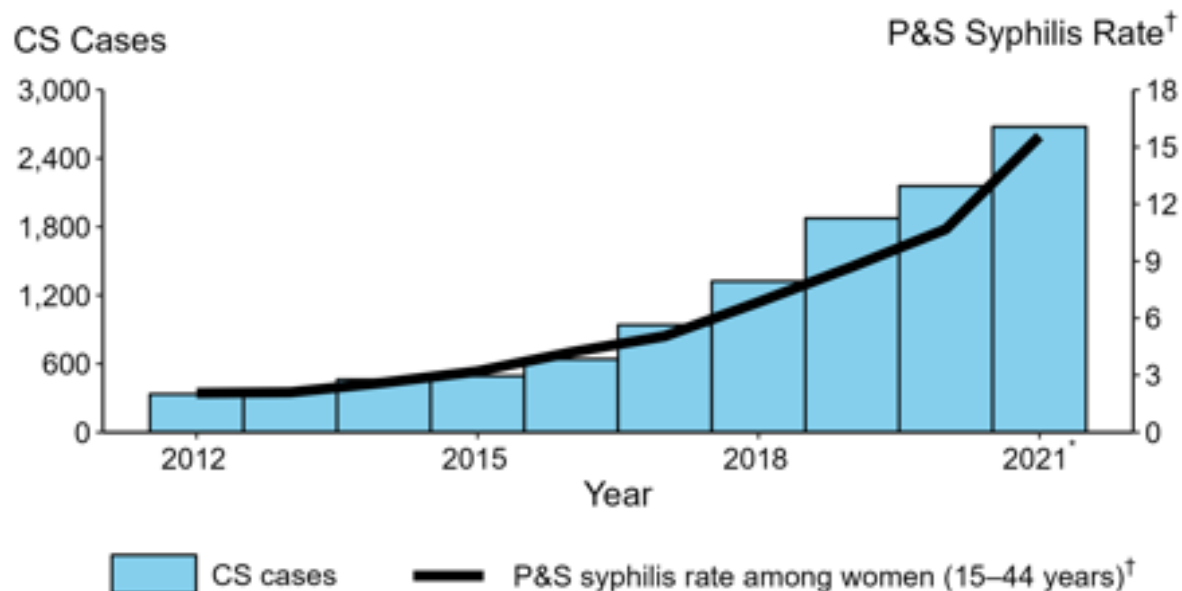
# Why is this happening?

- Multifactorial
  - Access to care
  - Increased risky behavior
    - Opioid and other drug epidemic
  - Missed opportunities
- Not due to drug resistance

# Syphilis Risk Factors

- Drug use
- Poverty
- High prevalence of syphilis in the community
  - AZ is 6<sup>th</sup> in the nation for syphilis rates
    - #2 for congenital infection rate
- Multiple sexual partners
  - California study 70% of women with syphilis had only 1 sexual partner within the last 12 months
  - NY study 32% acquired syphilis during pregnancy after initial negative test
- History of other STIs
  - But...NY study 91% had no additional STIs during pregnancy

## Congenital Syphilis — Reported Cases by Year of Birth and Rates of Reported Cases of Primary and Secondary Syphilis Among Women Aged 15–44 Years, United States, 2012–2021\*



\* Reported 2021 data are preliminary as of July 7, 2022

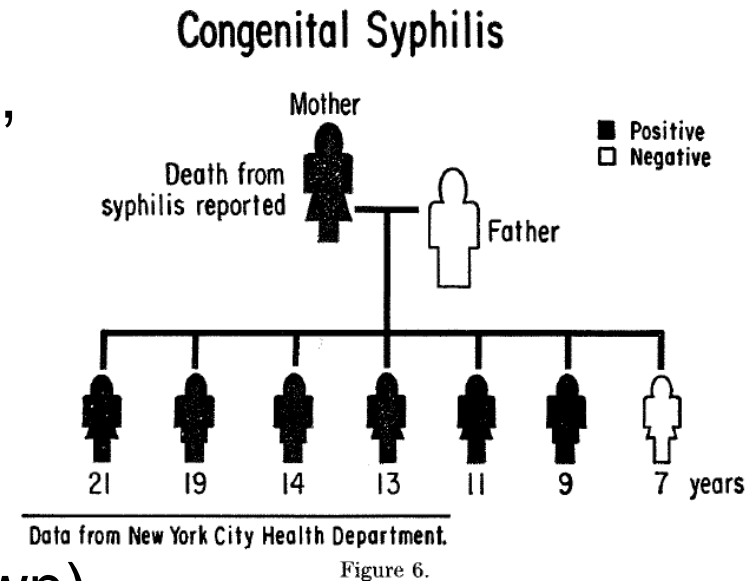
† Per 100,000

**ACRONYMS:** CS = Congenital syphilis; P&S = Primary and secondary syphilis



# Risk of Congenital Infection by Stage of Maternal Infection

- Primary (chancre)
  - 60-100%
- Secondary (systemic symptoms, rash, etc)
  - 60-100%
- Early latent (asymptomatic, infection within 1 year)
  - 40%
- Late Latent (asymptomatic, infection >1 year prior or unknown)
  - 8%



# Congenital Syphilis: A Preventable Disease

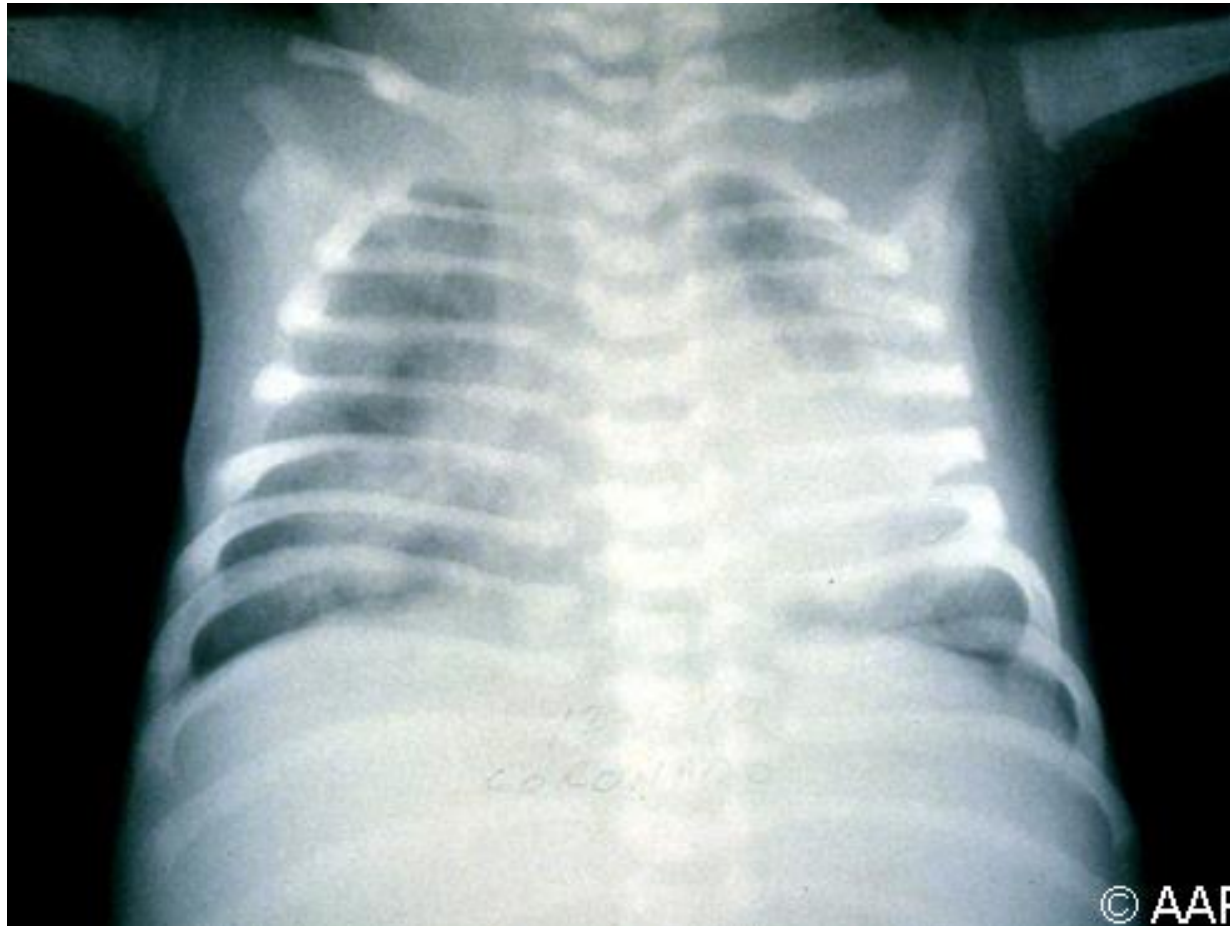
- 40% mortality rate
  - Spontaneous abortion, stillbirth, perinatal death
- Most common presentation is no signs/symptoms
  - Will usually progress to early or late manifestations if untreated
- Can affect any organ system with devastating effect
- Early signs/symptoms: within 2 years of birth
- Late signs/symptoms: after 2 years, usually around the time of puberty

# Patient with severe and multiple early manifestations

- 30 week gestation
- Mom used drugs during pregnancy, no prenatal care, syphilis diagnosed at delivery
- Baby with HSM, thrombocytopenia, coagulopathy
- Vitreous inflammation on ophtho exam

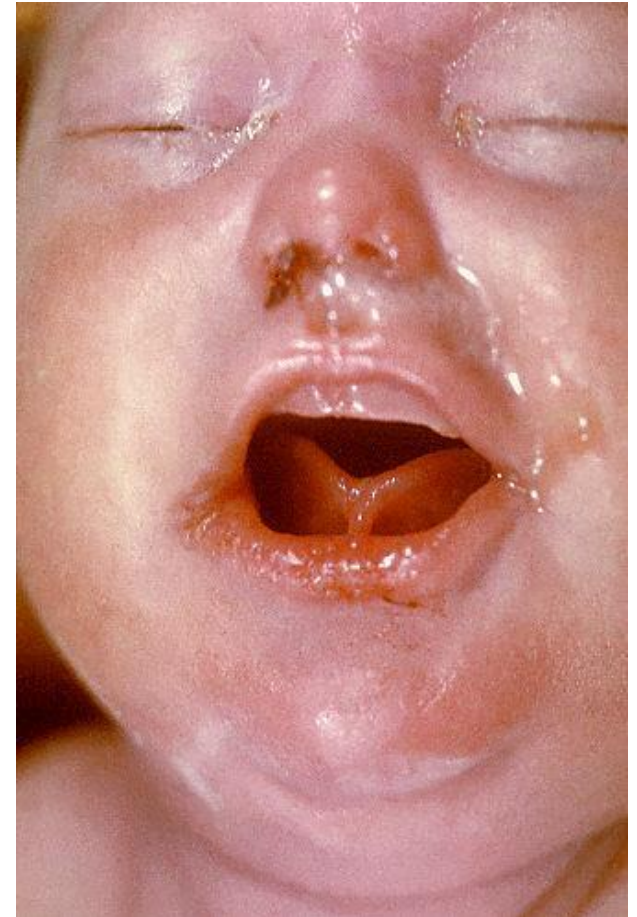


# Early manifestations: Pneumonia alba





# Snuffles and mucous membrane fissuring



# Early Manifestation: Osteitis



Our patient



Normal xray  
(term baby)

# Other Early Manifestations

- Other skin lesions
- CNS disease: often quiescent
- Ocular involvement
- Sensorineural hearing loss
- Adenopathy
- Nephrotic syndrome

# Missed case

- Few weeks old term baby admitted with flu, mildly elevated LFTs and “cradle cap”
- Mom had negative RPR early in pregnancy, never tested again
- Baby home after stable respiratory status













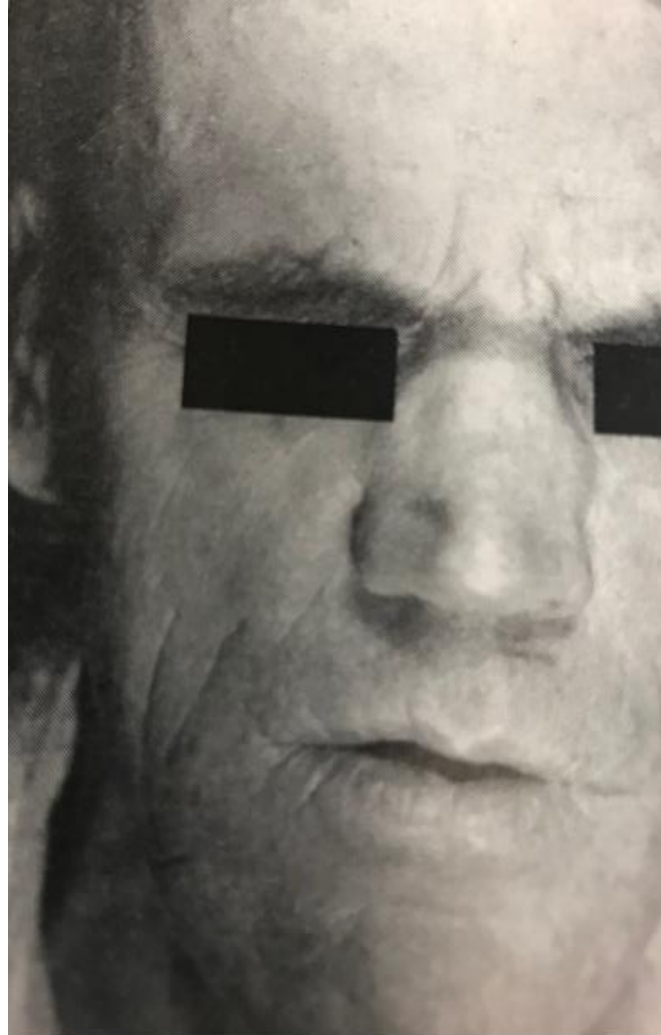
# Another missed case

- Mother had negative test early in pregnancy, never rechecked
- Baby asymptomatic at delivery
- Developed rash and pseudoparalysis





# Late Manifestations: Nose Deformity, Rhagades



Youmans 1964

# Late Manifestation: Interstitial Keratitis



# Late Manifestation: Hutchinson Teeth



# Late Manifestation: Mulberry Molars



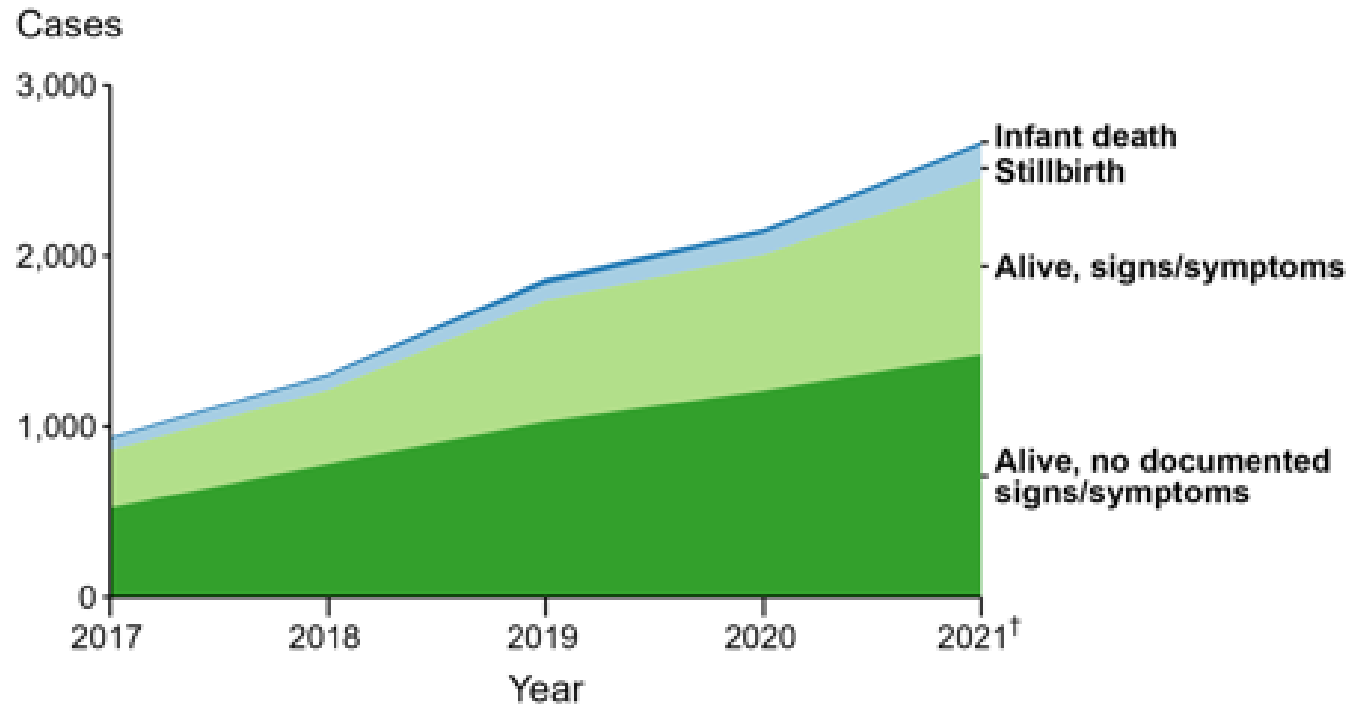
# Late Manifestation: Saber Shins



# Other Late Manifestations

- Sensorineural hearing loss
- CNS infection with or without long term neurologic deficit
- Cluttons joints
- And much more.....

# Congenital Syphilis — Reported Cases by Vital Status and Clinical Signs and Symptoms\* of Infection, United States, 2017–2021<sup>†</sup>



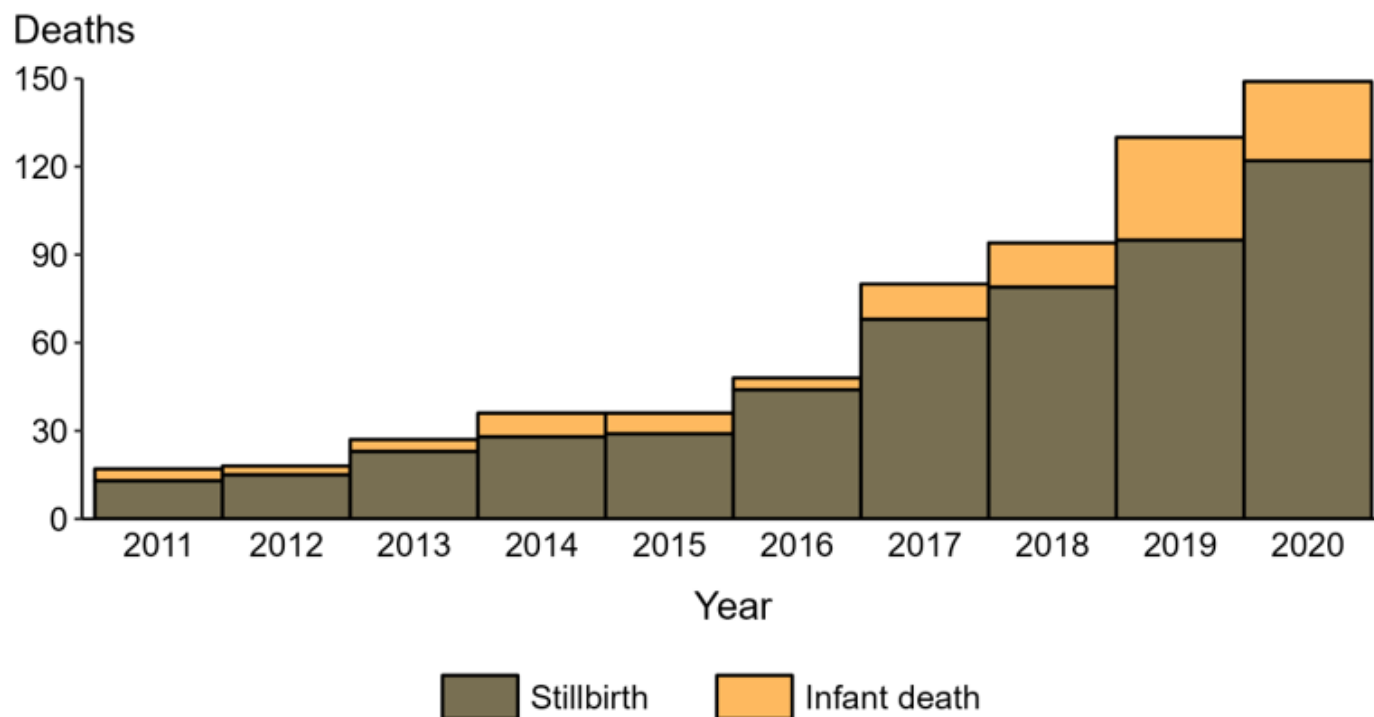
\* Infants with signs/symptoms of congenital syphilis have documentation of at least one of the following: long bone changes consistent with congenital syphilis, snuffles, condyloma lata, syphilitic skin rash, pseudoparalysis, hepatosplenomegaly, edema, jaundice due to syphilitic hepatitis, reactive CSF-VDRL, elevated CSF tRBC or protein, or evidence of direct detection of *T. pallidum*.

<sup>†</sup> Reported 2021 data are preliminary as of July 7, 2022.

NOTE: Of the 8,974 congenital syphilis cases reported during 2017 to 2021, 30 (0.3%) did not have sufficient information to be categorized.



## Congenital Syphilis — Reported Stillbirths and Infant Deaths, United States, 2011–2020

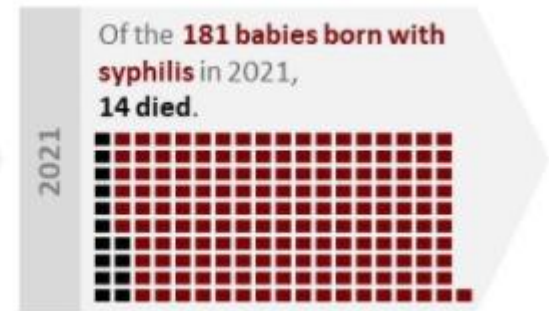
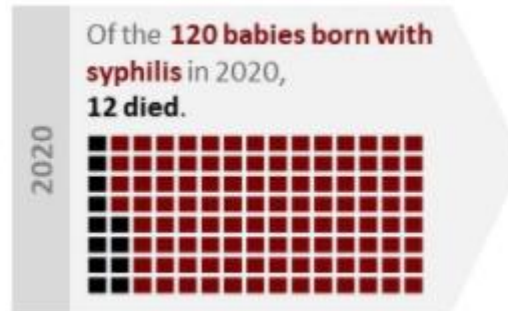
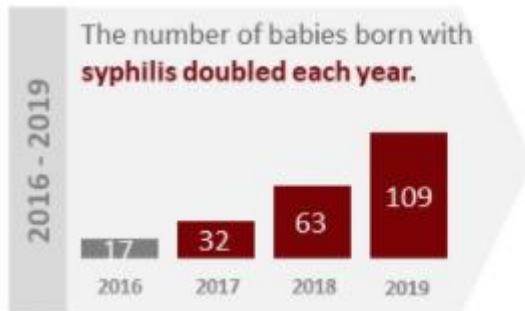
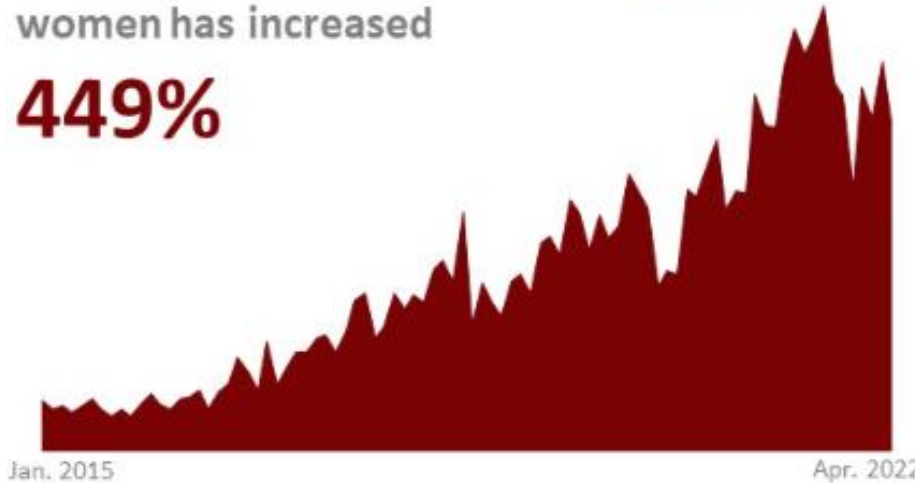




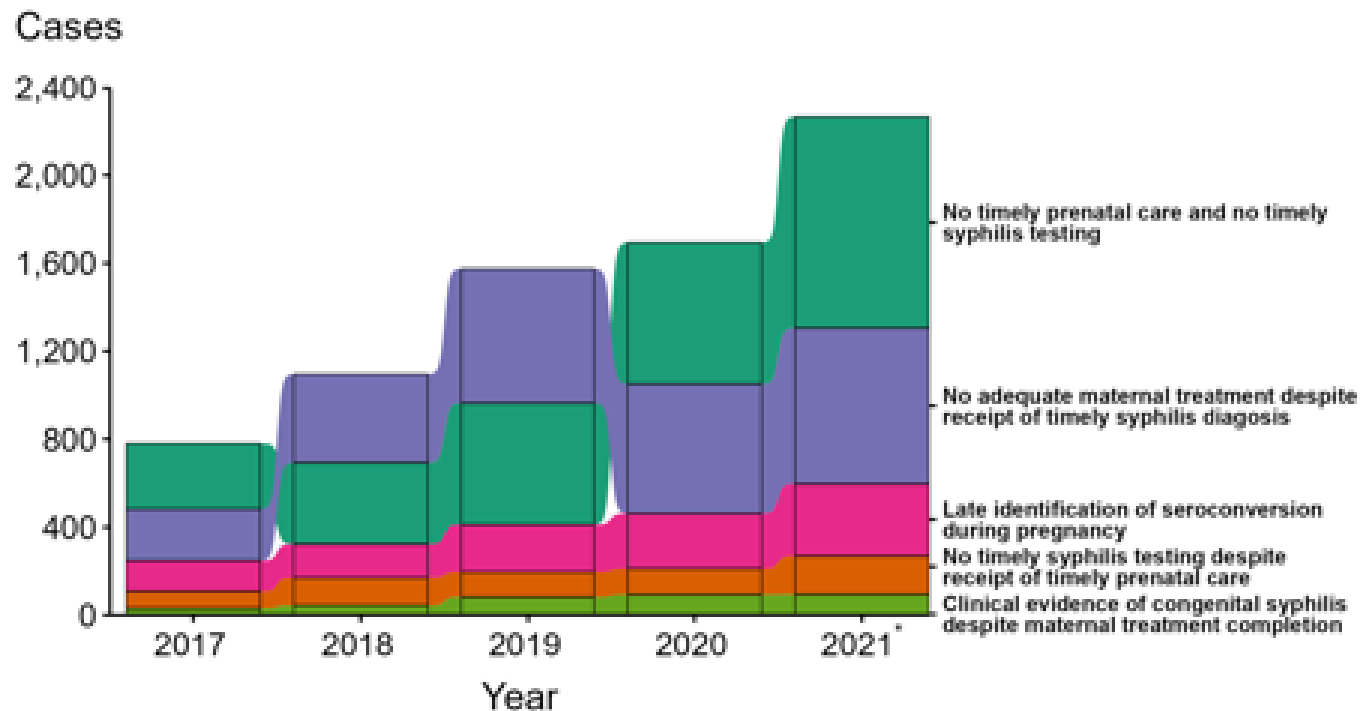
# Arizona's Syphilis Nightmare

Since 2015, the yearly average of **syphilis** cases in women has increased

**449%**



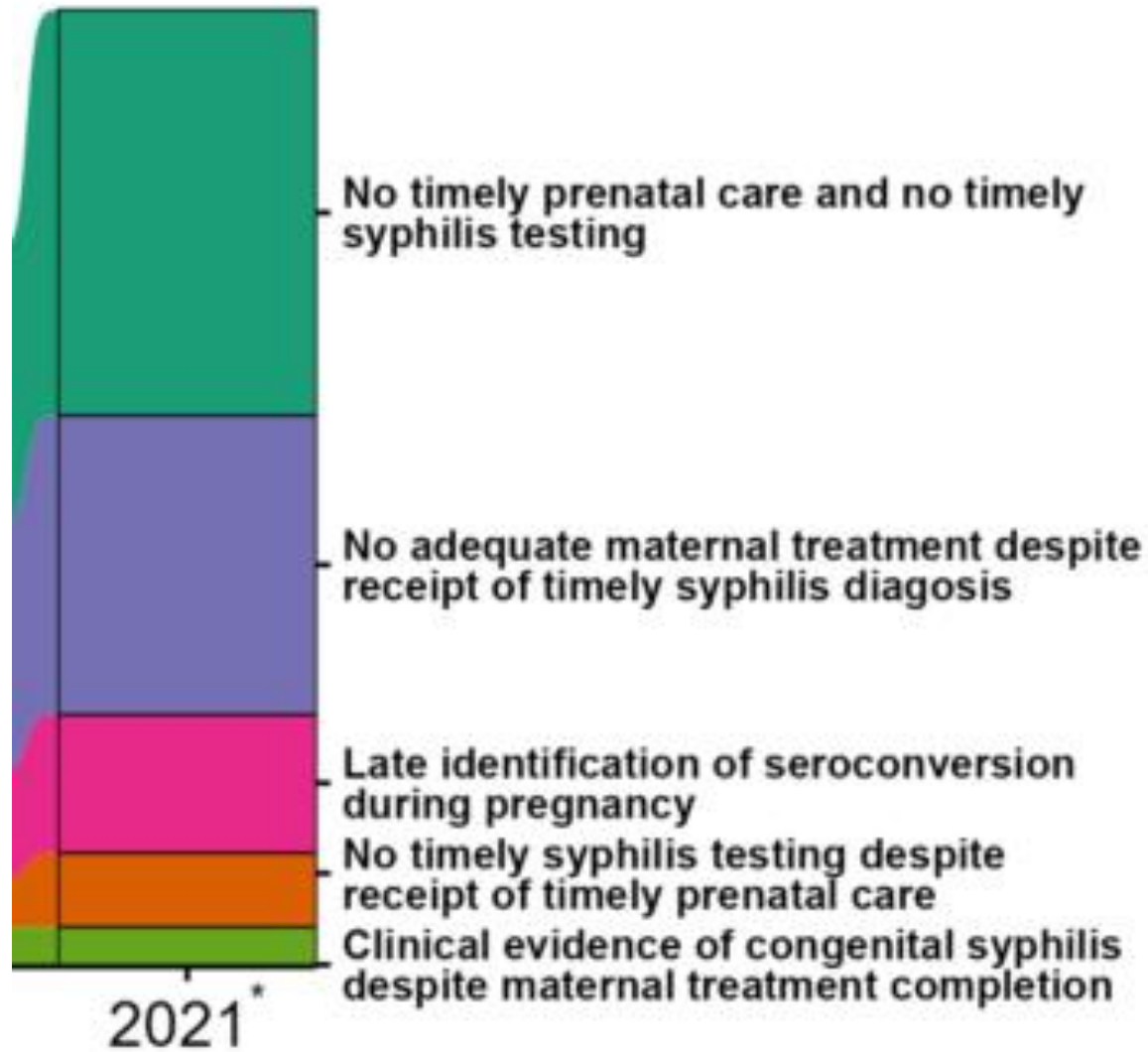
# Congenital Syphilis — Missed Prevention Opportunities among Mothers Delivering Infants with Congenital Syphilis, United States, 2017–2021\*



\* Reported 2021 data are preliminary as of July 7, 2022

**NOTE:** Of the 8,974 congenital syphilis cases reported during 2017 to 2021, 1,562 (17.4%) were not able to have the primary missed prevention opportunity identified due to insufficient information provided to CDC related to maternal prenatal care, testing, or treatment.





# The alphabet soup of syphilis diagnosis

- Antibody based, can cross react with other diseases
- Non treponemal (RPR or VDRL)
  - Antibody response (IgM and IgG to inflammation in syphilitic tissue)
  - Tend to increase with infection, decrease with treatment: can use to track response to therapy
  - Low titer false positives with viral infection, autoimmune disease, pregnancy
- Treponemal (TP-PA, FTA-ABS, MHA-TP, EIA, CIA)
  - Stay positive for years/possibly lifelong

# Syphilis diagnosis

- Old way
  - RPR (or VDRL) screen followed by confirmatory test (TP-PA) if positive
- New way (for some)
  - Screening EIA followed by RPR and/or TP-PA if positive
- Follow the RPR for response to therapy

# Congenital infection

- Screen, screen, screen
  - Infection later in pregnancy is possible
    - AZ: entry to care, early 3<sup>rd</sup> trimester, at delivery
    - About 30% of congenital syphilis cases occurred in mother with initial negative screen early in pregnancy
  - 60% infants have no visible sign of infection at birth
    - Develop signs/symptoms if untreated
  - Compare mom's RPR to baby's RPR
  - High risk situations: look for other abnormalities (CSF, CBC, long bone films, ophtho exam, etc)

# High risk for congenital infection

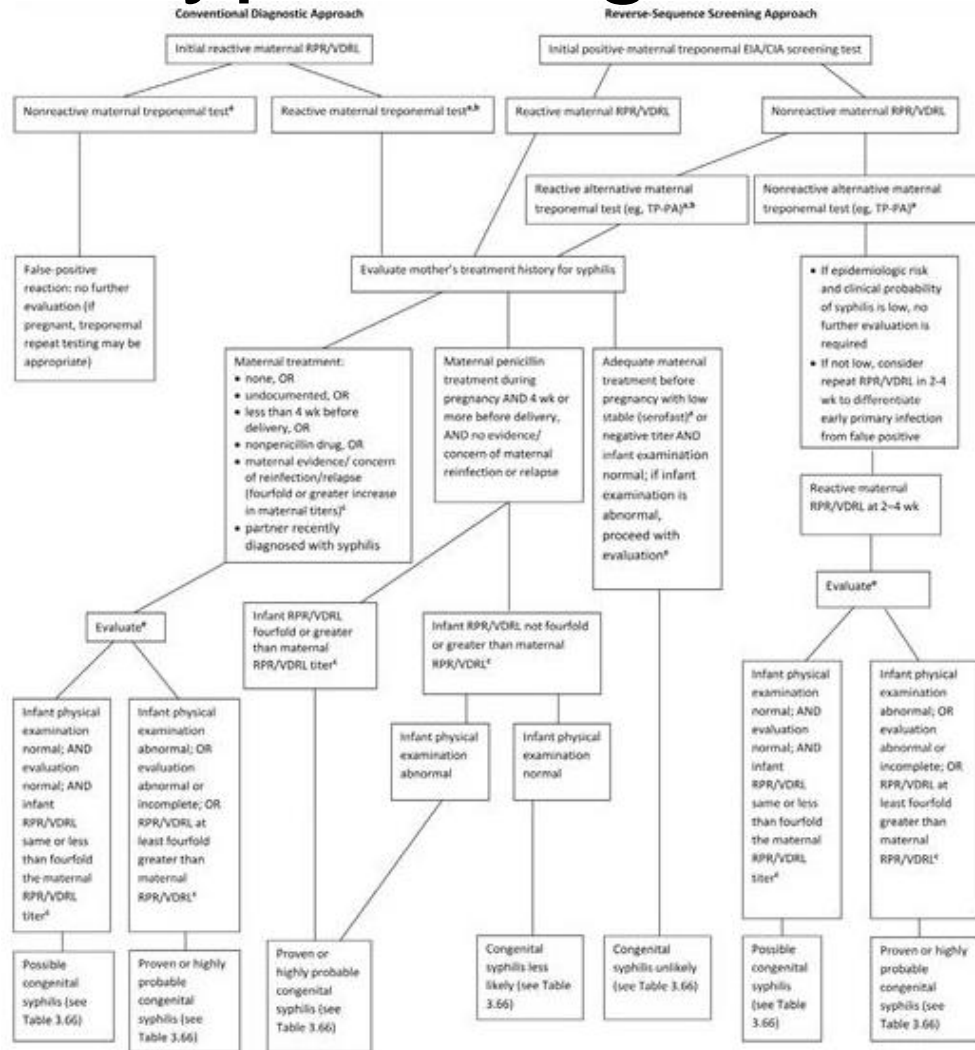
- Partner recently diagnosed with syphilis
- No maternal treatment during pregnancy
- Mom didn't get treated with penicillin
- Penicillin given <1 month before delivery
- Maternal RPR increased fourfold from pre-treatment titer
  - ie 1:4 increased to 1:16 (2 dilutions)
- Baby has exam findings concerning for syphilis

# Modern Treatment Regimens

- Penicillin is still the drug of choice
  - IM Benzathine PCN does not achieve long enough time above the MIC to treat CNS disease
    - Use IV aqueous penicillin G for CNS disease, congenital infection
  - PCN allergy
    - Non pregnant, non congenital infection
      - Desensitize and treat with PCN, or:
      - Ceftriaxone, doxycycline, azithromycin options with close follow up
    - Pregnant
      - Desensitize and treat with PCN



# The Complicated Congenital Syphilis Algorithm



# Congenital Infection?

- Proven or highly probable: 10 days IV PCN
- Possible: 10 days of IV PCN
- Less likely: IM PCN
- Unlikely: no PCN and follow RPR if maternal RPR positive
- Positive RPR: follow at 2, 4, 6 months
- Negative RPR: repeat at 3 months

# Non-Congenital Infection

- Primary, Secondary, Early latent
  - 1 dose IM benzathine penicillin, follow the RPR
- Late latent, tertiary
  - 3 doses IM benzathine PCN 1 week apart. Additional dose(s) if missed dose(s), follow the RPR
- Neurosyphilis
  - IV PCN 10-14 days, follow the RPR

# Fun with syphilis testing and treatment

- Scenario 1: Delivery
  - Mom EIA positive, RPR 1:4
    - Never been tested or treated for syphilis
      - Mom has syphilis
      - Will get 3 doses IM PCN (assume late latent since never before tested/treated)
  - Baby normal exam but RPR 1:16, rest of work up negative
    - Baby has congenital syphilis
    - Will get 10 days of IV penicillin
    - Follow RPR at 2, 4, and 6 months until negative

# Fun with syphilis testing and treatment

- Scenario 2
  - Mom RPR positive, titer 1:64, TP-PA positive at 1<sup>st</sup> trimester
    - No prior testing or treatment
    - Has syphilis
  - Mom treated appropriately with IM PCN x3
    - Repeat RPR are 1:16 at 24 weeks, then 1:4 at delivery
  - Baby RPR 1:2 and normal exam
    - Baby avoided syphilis
    - Still gets a dose of IM PCN and follow RPR at 2, 4, and 6 months just in case

# Fun with syphilis testing and treatment

- Scenario 3: Delivery
  - Mom RPR 1:32, TP-PA negative
    - Prior RPRs negative, asymptomatic, no prior STIs
      - False positive???
  - Father is not monogamous
  - Mom EIA is positive
    - She has syphilis and gets treated after baby born
  - Baby RPR is negative and work up for syphilis negative
    - Dodged a syphilis bullet
    - Still got treated with 10 days of IV PCN just in case since 60-100% risk of infection and can be asymptomatic early in infection

# Conclusion

- Syphilis is running rampant in many communities
- Highly treatable disease
- Penicillin still the drug of choice
  - Desensitize and treat during pregnancy
- Many missed opportunities to diagnose and treat

# References

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